REMARKS

As a preliminary matter, attention is directed to the Petition For Extension of Time of two months included herewith, which includes authorization to charge fees to the deposit account of Pfizer Inc.

It is believed that no new claim fees are owed because of the instant amendments. If the Office determines that additional fees are owed, however, please charge same to Deposit Account No. 16-1445. Two copies of this paper are enclosed.

Each of independent claims 1, 6, and 13 has been amended by incorporating claim 21 therein, and claim 21 has accordingly been canceled. The independent claims now state that the solid amorphous dispersion provides a maximum concentration of the CETP inhibitor in a use environment that is at least 10-fold the equilibrium concentration provided by a control composition consisting essentially of an equivalent amount of the CETP inhibitor but with no concentration-enhancing polymer. Support is also in the specification at page 11, lines 18-25.

Each of claims 20 and 22-24 has been changed by amending the dependency to be from claim 25. Each of the aforementioned claims has also been amended by changing the preamble to state that they further modify the "product" of claim 25 rather than the "method" of claims 1, 6, or 13.

Claims 1, 6 and 13 were rejected under 35 USC 112, first paragraph. The examiner contended that the specification, while being enabling for quinoline cholesteryl ester transfer protein inhibitors and carboxymethyl ethyl cellulose and polyoxyethylene-polyoxypropylene block copolymers as the concentration enhancing polymers, does not reasonably provide enablement for all cholesteryl ester transfer protein inhibitors and all concentration enhancing polymers.

The rejection is traversed on the basis that it is misplaced both factually and legally. Claims 1, 6, and 13 are directed to methods for preparing pharmaceutical compositions comprising a CETP inhibitor and a concentration-enhancing polymer. Numerous polymers in addition to those noted by the Examiner have been exemplified by Applicants - - HPMCAS (Example 1 and many others), HPMCP (Example 2), PVP (Example 3), CAT (Example 4), CAP (Example 5), HPMC (Example 6). The examples abundantly detail how to practice the invention with many more polymers than just the ones cited in the Office Action. Thus, Applicants have in fact well supported their invention, and the Examiner has provided no basis why the invention could not be practiced as broadly as claimed.

Further, the rejection is misplaced legally. The C.C.P.A. held in In re Marzocchi, 169 U.S.P.Q. 367 (C.C.P.A. 1971),

> "[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with enabling requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support."

Per Marzocchi, the burden is on the Examiner to come forth with evidence to establish a prima facie case in support of the rejection. Applicants' specification must otherwise be taken as presumptively enabling. For the instant rejection, no specific factual evidence (e.g., publications) has been presented to establish a prima facie case pertaining to §112. Therefore, the statements in the present application must be taken as the truth. In re Marzocchi, supra at 369. Applicants respectfully submit that the invention has been well enabled and request that the §112 rejection be withdrawn.

Claims 20-24 were objected to under 37 CFR 1.75(c) as being of improper form, the Examiner having taken the position that the claims do not further limit the subject matter of a previous claim. Although Applicants do not agree with the objection, the dependence of the claims 20 and 22-24 has been changed to be from (product) claim 25 in order to expedite prosecution. Claim 21 has been canceled. Withdrawal of the objection is accordingly respectfully requested.

Claims 1-5 and 13-25 were rejected under 35 USC 102(b) as being anticipated by Miyajima et al. (US 4,983,593). The examiner stated, in pertinent part:

> Miyajima discloses the preparation of pharmaceutical composition that comprises NZ-105 and hydroxypropylmethylcellulose acetate succinate (HPMCAS) (abstract), a concentration-enhancing polymer. NZ-105 inhibits the activity of cholesteryl ester transfer protein (see Kitahara et al and Toyoda et al as teaching references). The preparation process as disclosed by Miyajima involves dissolving NZ-105 and HPMCAS in an organic solvent, removing the solvent by means of vacuum drying, freeze-drying; the NZ-HPMCAS is spray coated (column 3, line 55 to column 4, line 57). It is known that "spray drying is used conventionally and broadly refers to processes involving breaking up liquid mixtures into small droplets (atomization)...droplets" (paragraph [0049] of page 8 of EP 0 901 786, as teaching reference, which is of similar importance in the instant claims). Molten mixtures generally form when samples are frozen for freeze-drying. The methods recited in claims 20-24 do not limit the method steps in the preparation of pharmaceutical composition but these claims rather recite the properties of the formulation formed by the method and have been examined as claims defining the properties of the formulation formed by the process; the properties are inherent to the composition and cannot be separated from the composition. Specifically, it is noted that no specific cholesteryl ester transfer

> protein inhibitors and concentration enhancing polymers are claimed that would otherwise have distinct properties resulting from either the amounts/concentration of the drug-polymer product. Claim 25 is any product formed between the cholesteryl ester transfer protein inhibitors and concentration enhancing polymers. Miyajima meets the limitations of the claims. [8/11/04 Office Action, pages 4-5]

The rejection is traversed on the basis that NZ-105 is not a CETP inhibitor, and that Miyajima does not disclose one otherwise or suggest that CETP inhibitors generally would have utility in the instant invention. Miyajima as a reference dealt with only one compound, NZ-105, also known as efonidipine. He clearly sought to make an invention for that one compound which, as discussed below, is not a CETP inhibitor. Thus Miyajima does not disclose all elements of the claimed invention, hence cannot anticipate.

The Examiner based the rejection in part on the allegation that NZ-105 is a CETP inhibitor, citing the Kitahara and Toyoda abstracts as teaching references to support her position. That position is untenable since both abstracts in fact teach the opposite.

First, realize that CETP inhibition results in altering plasma lipid levels, specifically raising HDL and lowering LDL cholesterol. This in fact is unequivocally highlighted by Applicants in their introductory remarks in the specification:

> This invention relates to cholesteryl ester transfer protein (CETP) inhibitors...and the use of such inhibitors to elevate certain plasma lipid levels, including high density lipoprotein (HDL)-cholesterol and to lower certain other plasma lipid levels, such as low density lipoprotein (LDL)-cholesterol and triglycerides and accordingly to treat diseases which are affected by low levels of HDL cholesterol and/or high levels of LDL-cholesterol and triglycerides, such as atherosclerosis and cardiovascular diseases in certain mammals (i.e., those which have CETP in their plasma) including humans. (Specification, page 1, lines 10-21)

To the contrary, Toyoda discloses that efonidipine (NZ-105) does the opposite:

> These results suggest that NZ-105 may suppress the development of atherosclerosis without affecting the plasma lipids. (Toyoda et al., last sentence)

Thus, whatever NZ-105 is doing in Toyoda et al. to benefit atherosclerosis, it is disclosed as being independent of affecting plasma lipid levels, i.e., exactly the opposite of the effect CETP inhibitors are known and expected to have. Toyoda otherwise discloses nothing that would support NZ-105 being a CETP inhibitor. The only utility attributed to

NZ-105 by Toyoda is that it is a dihydropyridine calcium antagonist, a utility associated with lowering blood pressure. Although high blood pressure (hypertension) is a well-known independent risk factor for developing atherosclerosis, that factor is independent of any action on CETP. Thus the only utility attributed by Toyoda to NZ-105 is that of being a calcium antagonist, a utility unrelated to affecting plasma lipids, which Toyoda et al. disavow in any event.

Kitahara et al. are even more peripheral than Toyoda. Kitahara et al. describe the effects of efonidipine (NZ-105) on cholesterol ester metabolism, induced by beta-migrating very low density lipoprotein (beta VLDL) in J774 macrophages. J774 macrophages are mouse macrophages, a species that does not produce or contain CETP. Kitahara et al. disclose nothing otherwise relating to CETP inhibition and, like Toyoda et al., simply note that it is a calcium antagonist. Kitahara concludes that "...efonidipine suppresses cholesterol ester deposition ...mainly through elevation of the cellular cyclic AMP level". CETP inhibition is unrelated to elevating cyclic AMP levels which, in turn, is unrelated to affecting plasma lipid levels.

To summarize, CETP inhibition unequivocally relates to affecting plasma lipids, specifically raising HDL and lowering LDL cholesterol. Toyoda et al. specifically state that NZ-105 has no effect on lipid levels. Kitahara et al. studied cholesterol esterification in cells (mouse macrophages) that do not contain CETP and attributed the effects of NZ-105 to a mechanism having nothing to do with CETP inhibition. Clearly, neither abstract supports that NZ-105 is a CETP inhibitor, and in fact support that it is not.

Claims 6-12 were rejected under 35 USC 103(a) as being unpatentable over Miyajima et al (US 4,983,593) in view of Nakamichi et al (US 5,456,923). The Examiner commented, in pertinent part, as follows:

> Miyajima discloses the instant method for forming the pharmaceutical composition. Miyajima does disclose using an extruder. Nakamichi discloses the use of twin-screw extruder to form solid dispersion of mixtures of cardiovascular system drug and concentration enhancing polymers such as hydroxypropylmethylcellulose acetate succinate (HPMCAS or AQOAT) (abstract, column 1, line 54 to column 2, line 59 and claims 1 and 2).
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> Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the method of Miyajima to form pharmaceutical composition of cholesteryl ester transfer protein inhibitors and concentration enhancing polymers. One having ordinary skill in the art would have been motivated to modify the process of Miyajima by passing the mixture thorough a twin-screw extruder according to the disclosure of Nakamichi with the expectation of heating the mixture below the decomposition temperature of the

polymer and the drug during the production of the solid dispersion. [Office Action, pages 5-6]

The rejection is traversed on the basis that it is (1) based on hindsight and (2) not supported by the references.

One of the underpinnings of this invention is that CETP inhibitors constitute a class of compounds that has poor aqueous solubility, and that has correspondingly low bioavailability. Much of the technology directed to improving the solubility and/or concentration of drugs generally has had only limited success when applied to CETP inhibitors. In this regard, and to provide useful background information against which the non-obviousness of Applicants' invention can be assessed, the following text is a quotation taken directly from the specification because it offers insights into the problems that Applicants have solved:

> However, it has proven difficult to formulate CETP inhibitors for oral administration such that therapeutic blood levels are achieved. CETP inhibitors in general possess a number of characteristics which render them poorly bioavailable when dosed orally in a conventional manner. CETP inhibitors tend to be quite hydrophobic and extremely water insoluble, with solubility in aqueous solution of usually less than about 10 μg/ml and typically less than 1 μg/ml. Often, the aqueous solubility of CETP inhibitors is less than 0.1 μg/ml. Indeed the solubility of some CETP inhibitors is so low that it is in fact difficult to measure. Accordingly, when CETP inhibitors are dosed orally, concentrations of CETP inhibitor in the aqueous environment of the gastrointestinal tract tend to be extremely low, resulting in poor absorption from the GI tract to blood. The hydrophobicity of CETP inhibitors not only leads to low equilibrium aqueous solubility but also tends to make the drugs poorly wetting and slow to dissolve, further reducing their tendency to dissolve and be absorbed from the gastrointestinal tract. This combination of characteristics has resulted in the bioavailability for orally dosed conventional crystalline or amorphous forms of CETP inhibitors generally to be quite low, often having absolute bioavailabilities of less than 1%.
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> Various attempts have been made to improve the aqueous concentration of CETP inhibitors , but generally have met with limited success. At the outset, most methods aimed at enhancing aqueous concentration and bioavailability of low-solubility drugs offer only moderate improvements. Such improvements generally lead to enhancements in aqueous concentration on the order of from one to seven fold. In addition, the enhancement may be short-lived, with the drug concentration returning to the equilibrium concentration within ten to 40 minutes. Such small, short-lived concentration enhancements have led to even lower levels of bioavailability enhancement when tested *in vivo* via oral administration. Thus, when conventional dosage forms of low-solubility drugs are tested *in vivo* via oral administration, bioavailability enhancements are typically on the order of 2-fold to 4-fold or less. For CETP inhibitors having low absolute bioavailabilities, such small improvements are insufficient to allow

convenient oral dosing of CETP inhibitors; that is, dosage forms having a convenient size and frequency of dosing.

Moreover, some standard methods for improving the concentration of pharmaceuticals in aqueous solution have proven inadequate when applied to CETP inhibitors. For example, even pre-dissolving the CETP inhibitor in a water miscible solvent such as polyethylene glycol followed by delivery as a solution to an aqueous environment of use has failed to raise the aqueous concentration of CETP inhibitor to an acceptable level. [Page 3, line 8 to page 4, line 21 of Applicants' specification]

Neither Miyajima nor Nakamichi discloses CETP inhibitors. Consequently, neither reference is capable of disclosing that any CETP inhibitor, much less CETP inhibitors as a class, would have a greatly improved maximum concentration by virtue of being formed as a solid amorphous dispersion by any of Applicants' claimed methods. Neither reference discloses or suggests that Applicants compositions would produce such good results, namely that a 10-fold maximum concentration (i.e., relative to a control containing no polymer) could be achieved with CETP inhibitors in a solid amorphous dispersion. Combining the references does nothing to change the conclusion of non-obviousness. Nakamichi relates to using twin screw extrusion, but is silent about CETP inhibitors for use with that method. Miyajima mentions a number of methods for combining a single compound, NZ-105, with HPMCAS, but says nothing relating to any CETP inhibitor individually or to CETP inhibitors as a class, much less anything that would render a 10-fold increase in CETP inhibitor maximum concentration obvious. The Examiner has provided no basis whereby one of ordinary skill in the art would find it obvious to use Applicants' methods to produce compositions that increase the maximum concentration of CETP inhibitors by such a large factor.

Indeed, because the references fail to disclose CETP inhibitors, their problematic low aqueous solubility, or any way of achieving a 10-fold improvement in aqueous CETP inhibitor maximum concentration, the only way that Applicants' invention could possibly be obvious is through an impermissible hindsight analysis. The Examiner appears to have imputed the missing teachings, individually and in combination, to the references when, in fact, they and their combination were disclosed only by Applicants. It is respectfully submitted that, by that analysis, the Examiner has fallen "victim to the insidious effect of a hindsight syndrome wherein that which the invention taught is used against its teacher." *W.L. Gore & Associates v. Garlock, Inc.*, 721 F.2d. 1540, 1553 (Fed. Cir. 1983). It is otherwise well-accepted law that it is impermissible to use the inventor's disclosure as a road map for selecting and combining prior art disclosures.

Grain Processing Corp. v. American Maize-Products Corp., 5 USPQ2d, 1788 (Fed. Cir. 1988). That law is even more applicable when Applicants' own disclosure has been used to supply disclosure. Again, neither Miyajima nor Nakamichi discloses any CETP inhibitor or suggests any method for improving the maximum concentration of CETP inhibitors in a use environment by 10-fold. Clearly, given the factual setting in which the invention as a whole was made, and based on the legal standards reviewed above, Applicants' invention is non-obvious, hence patentable.

Accordingly, it respectfully requested that the §103 rejection over Miyajima in view of Nakamichi be withdrawn.

No additional issues are seen to be outstanding, and in view of the foregoing comments and amendments, this case is believed to be in condition for allowance. A Notice of Allowance is courteously solicited.

Respectfully submitted,

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